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ORIGINAL RESEARCH

A Retrospective Case Series Of High-Intensity Focused Ultrasound (HIFU) In Combination With Gemcitabine And Oxaliplatin (Gemox) On Treating Elderly Middle And Advanced Pancreatic Cancer

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Purpose: This retrospective study was conducted to evaluate the safety and efficacy of high-intensity focused ultrasound (HIFU) ablation combined with Gemcitabine and Oxaliplatin (Gemox) for the treatment of middle and advanced pancreatic cancer in elderly patients.

Methods: Forty-seven patients with pancreatic cancer treated with HIFU and Gemox were evaluated for inclusion, and 38 cases were finally included. The primary endpoint was safety. Secondary endpoints included the response rate, the clinical benefit response (CBR), overall survival (OS), progression-free survival (PFS).

Results: After combination therapy of HIFU and Gemox, severe complications were rarely reported, and no treatment-related death occurred. The rate of three or four-degree myelosuppression was low, and no obvious impairment of hepatorenal function was observed. Pancreatitis and gastrointestinal injury did not occurred. The disease control rate (DCR) was estimated to be 76.3%, including complete remission (CR), partial remission (PR), stable disease (SD) in 1, 6, 22 cases, respectively. And the objective response rate (ORR) was 18.4%. The clinical benefit rate (CBR) was 68.4%, with the pain significantly relieved ($P<0.01$). The serum level of CA19-9 showed significant changes after HIFU treatment. The median overall survival (OS) was 12.5 months, with a 6-month and 12-month OS rate of 82.13% and 59.34%, respectively. Stratified analyses did not reveal any significant difference between patients in different stages.

Conclusion: Elderly patients (≥ 60 years old) with pancreatic cancer would experience tolerable toxicity and obtain good clinical benefits from the combination therapy of HIFU ablation and Gemox.

Keywords: high intensity focused ultrasound, Gemox, advanced pancreatic cancer, overall survival, elderly

Introduction

Pancreatic cancer is one of the highly prevalent malignant tumors with poor long-term prognosis[1] It is predicted that the new cases would be 56,770 in the United States in the year 2019. Moreover, the number of cancer-related deaths will be as high as 45,750[2] More than 80% of patients with pancreatic cancer die within a few months after the initial diagnosis, while less than 10% of patients are expected to

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survive more than five years[3] Most patients with pancreatic cancer are often in the advanced stage and unresectable at the time of diagnosis,[4,5] and this would mainly contribute to the decreased survival.[6] In recent years, the incidence rate in China, especially in the urban areas, has shown an upward trend, of which 2/3 patients are >65 years old. The median survival of untreated pancreatic cancer is only 3 to 4 months.[7]

Systemic chemotherapy (FOLFIRINOX) is the treatment of choice for patients with unresectable advanced pancreatic cancer as a potential role for consolidative radiation, yet overall survival remains low compared with those who are eligible for upfront surgical resection, notwithstanding recent advances in chemotherapy and radiation therapy. FOLFIRINOX is seldom used in China, as few patients could tolerate this regimen.The safety and efficacy of the Gemox regimen (gemcitabine and oxaliplatin) have been evaluated by numbers of studies as first-line therapy in patients with metastatic or unresectable locally advanced pancreatic cancer.[8–12] The objective response rate was 10–30%,[13] and the median overall survival was lower than one year.[14] Gemox in combination with other therapies, such as erlotinib,[15] tomotherapy,[16] bevacizumab[17] were also be evaluated.

High-intensity focused ultrasound (HIFU) is a non-invasive, conformal ablation technique developed in the past two decades and rapidly popularized in China. It can focus ultrasound energy on the target lesions and induces tumor coagulation necrosis by thermal effect.[18] HIFU also have non-thermal effects including cavitation through the generation and collapse of gas-filled bubbles in an ultrasound field) and mechanical tissue disruption by generating boiling bubbles.[19] Besides, the immunomodulatory function of HIFU has also been reported.[20,21] In the pancreas, the local treatment of cancer shows a unique advantage.[22] Several clinical trials of HIFU palliative therapy for pancreatic carcinoma cases have provided promising results.[23,24] HIFU monotherapy[25–30] or in combination with systemic chemotherapy[31,32] have been proved to be able to relieve pain and might bring an additional survival benefit with rare severe adverse events.

HIFU ablation combined with Gemox for pancreatic cancer has not been investigated by previous study. This retrospective case series analysis was conducted to evaluate the safety and feasibility of combination therapy of HIFU ablation and Gemox for the treatment of elderly patients with unresectable middle and advanced pancreatic cancer.

Materials And Methods

Patients

From March 2012 to March 2016, newly diagnosed unresectable middle and advanced pancreatic cancer patients were eligible for treatment in our center. The diagnostic criteria should meet at least one of the following conditions: (1) biopsy of pancreatic tumor during surgical exploration, pathological confirmation; (2) percutaneous puncture under ultrasound guidance, pancreatic occupying tissue, pathological confirmation; (3) patients who cannot obtain pathological evidence must have typical Imaging findings, or evidence of liver or retroperitoneal lymph node metastasis, accompanied by increased peripheral blood CA19-9.

The inclusion criteria were as follows: (1) patients aged ≥ 60 years old; (2) patients with adequate liver, kidney, and bone marrow function (white blood cell ≥ 3.9×10^9/L, absolute neutrophil count ≥ 1.5×10^9L, platelets ≥ 100×10^9/L, hemoglobin ≥ 10g/dL, and serum creatinine ≤ 150mmol/L); (3) patients with Karnofsky Performance Status (KPS) of ≥ 60 points and expected survival of > 3 months. All patients had no possibility of radical resection (tumor could not be removed; patients could not tolerate radical surgery or patients refused surgery). Some cases should be excluded, including poorly controlled diabetes, prior cerebrovascular event, active second malignancy, and uncontrolled intermittent illness. Besides, patients with tumor size > 10 cm were also excluded as they were not suitable for HIFU treatment.

The research obtained the approval of the ethics committee of Xinhua Hospital affiliated to Shanghai Jiaotong University and was done according to the Declaration of Helsinki.

Procedure

Patients with jaundice should receive percutaneous transhepatic cholangiography/gallbladder drainage (PTCD/PTGD) or endoscopic retrograde cholangiopancreatography (ERCP) prior to HIFU.

HIFU treatments were performed using the instrument of HIFUNIT-9000 (Shanghai Aishen Sci-Tec Co., Ltd.). The equipment parameters: sound intensity (I) = 3000 ~ 8000W/cm^2, focal spot = 3mm × 3mm × 8mm; power: 60%~100%; unit launch time: 0.15 ~ 0.2s, interval time (t2): 0.3 ~ 0.4s, t1: t2 = 1: 2; single point of treatment (n): 8 ~ 14 times; number of transducers (T): 3 to 6. Before treatment, according to the location, size, shape of the lesion, and the relationship with adjacent organs,

combined with the general situation of the patient to develop a preliminary treatment plan. The patient was fasted to gas-producing food three days before treatment and fasted and banned water in the morning of treatment. During treatment, the patient should be placed in the supine position without anesthesia (Figure 1A). The position of the lesions was firstly determined by b-mode sonography, CT, MRI, or PET/CT. Then the re-localization of the therapy area was completed through the built-in detecting head of the instrument. The US monitoring system was started, and the treatment range was defined according to the real-time image, by ascertaining the treatment levels and power. After setting up the treatment parameters, the treatment focus was moved following the X, Y and Z axes in terms of the planned procedure to cover the entire predetermined target regions. Each treatment time is 30 to 40 mins, once a day, five times in a row. If the tumor is difficult to cover the scan within five sessions, the number of treatments was added until the predetermined target area was completely covered.

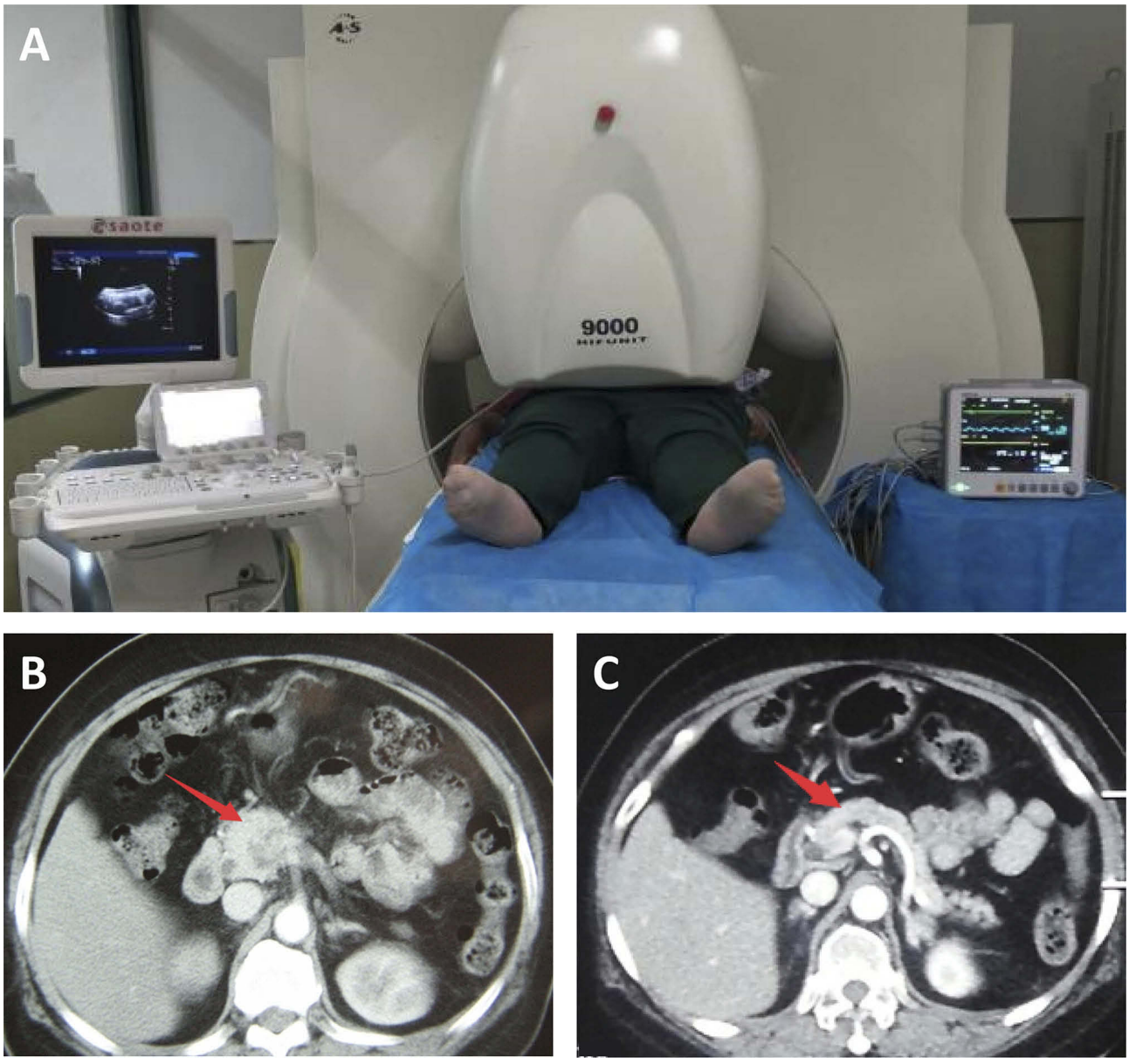

Figure 1 Treatment process and CT imaging of a 65-year-old male patient with pancreatic cancer who received HIFU treatment.
Notes: (**A**) This patient was receiving HIFU ablation in a supine position. (**B**) Before treatment, a space-occupying lesion with a diameter of about 2 cm could be seen in the pancreatic uncinate process, without pancreatic duct dilated. The CA 19–9 level was tested to be 4370 U/mL. (**C**) Six months after HIFU treatment, the size and morphology of the pancreas returned to normal, and no visible space-occupying lesions were found in the uncinate process. The CA 19–9 level reduced to 362 U/mL.
Abbreviations: CT, computed tomography; HIFU, high-intensity focused ultrasound.

One cycle of chemotherapy was given on the first day after HIFU ablation. The chemotherapy regimen was Gemox: gemcitabine 1000 mg/m^2, day 1 and day 8; oxaliplatin 135 mg/m^2, day 1; 21 days for a chemotherapy cycle. Changes in peripheral blood, liver and kidney function, and electrocardiogram were measured during chemotherapy. Each patient completed at least 3 cycles of chemotherapy.

Outcomes And Measurements

The primary endpoint was the safety of HIFU and Gemox. Chemotoxic side effects were evaluated according to the NCI Common Toxicity Grading Standard Version 3.0.[33]

The secondary endpoints included best overall response, clinical benefit rate (CBR), overall survival (OS), progression-free survival (PFS). The response rate was evaluated by self-determination criteria, which was combination of the response evaluation criteria in solid tumor (RESIST 1.1) established by the American Cancer Institute (NCI)[34] and the specificity of pathological changes after HIFU ablation. Complete response (CR): the lesion completely disappears and remains more than 4 weeks; partial response (PR): the sum of the maximum diameter of the lesion is reduced by ≥ 30% and maintained for more than 4 weeks; progression disease (PD): The sum of the maximum diameters of the lesions increased by ≥20% or new lesions appeared; stable disease (SD): the lesion shrinks less than PR or increases to PD. Patients achieved CR, PR, and SD were both considered as effective. Because the tumor tissue is mostly coagulative necrosis after HIFU ablation, the tumor is reduced by <30%, and the tumor in a stable state was also regarded as therapeutically effective. CBR was assessed based on the following criteria: (1) pain is reduced by ≥50% for more than 4 weeks, (2) the amount of analgesic medication is reduced by ≥50% for more than 4 weeks, (3) the improvement of KPS score is ≥20 points for more than 4 weeks, (4) and the weight gain is ≥7%. At least one of these items exceeds the above criteria with the others stable was consider as valid. Otherwise, it was invalid.[35]

As to the heterogeneity between the patients in different stages, subgroup analyses were also conducted by us to describe the results in more detail.

Patients' Follow-Up

The OS and PFS were defined as the duration between the date of all-cause death and disease progression or death, respectively, from the end of HIFU intervention. Censoring occurred if patients were still survival at the last follow-up. Peripheral blood CA19-9 was examined every four weeks during the first year after HIFU combined with chemotherapy. The pain was evaluated by using the visual analogue scale (VAS) method at 1 month after HIFU ablation and then 3-month intervals during the follow-up.[36] Tumor size was measured by computed tomography (CT) or magnetic resonance (MRI) methods. Response evaluation was performed at 1 month and 3 months after HIFU and then 3-month intervals during the first year and 6-month intervals during the remainder of the follow-up phase. The best overall response was reported.

Statistical Methods

Data analyses were performed using STATA 12.0 statistical software (Stata Crop, Lakeway Drive College Station, USA). Normally distributed data were presented as mean ± standard deviation. Non-normally distributed data were expressed with a median (range). The independent Student's t-tests or Wilcoxon tests were used to compare data between each time point after treatment and baseline, as appropriate. Median OS and PFS with 6 and 12-month survival rates were calculated by the Kaplan-Meier method. Chi-square tests were conducted to compare results between different clinical stages in the subgroup analyses. The P<0. 05 indicates that the difference was statistically significant.

Results

Characteristics Of Patients

Forty-seven patients were retrospectively evaluated for inclusion. Thirty-eight patients of them were included finally, with a median age of 69 years (range: 60–78), including 21 males and 17 females. Twenty-eight cases were confirmed by surgical or biopsy histopathology, and 10 cases were diagnosed with pancreatic cancer based on clinical signs, imaging, and serum radioimmunoassay. The tumors were located in the head, body, and tail of the pancreas in 16, 13, and 9 cases, respectively. KPS score ≥ 80 was seen in 17 patients. According to the Union for International Cancer Control (UICC) clinical stage:[37] stage II, stage III, and stage IV pancreatic cancer were confirmed in 4, 15, and 19 cases, respectively. All the cases with occupying diameter were larger than 1cm (the built-in probe with a diameter of less than 1cm is difficult to detect), and the largest tumor was 8.4×6.0cm (Table 1).

Table 1 Patient Baseline Characteristics

Characteristics	Characteristics	No. Of Patients (%/Range)
Gender	Male Female	21 (55.3%) 17 (44.7%)
Age	Median (range), years	69 (60–78)
KPS	Mean±SD ≥ 80 < 80	72.63±10.27 17 (44.7%) 21 (55.3%)
VAS	Mean±SD ≥ 4 <4	5.86±2.13 29 (76.3%) 9 (23.7%)
Tumor location	Head Body Tail	16 (41.2%) 13 (33.3%) 9 (23.7%)
UICC-Stage	Stage II Stage III Stage IV	4 (10.5%) 15 (39.5%) 19 (50.0%)
Tumor size*	Mean±SD, cm ≥ 3cm < 3cm	4.2±1.6 22 (57.9%) 16 (42.1%)
CA 19-9	Mean±SD, U/mL Positive Negative	247.9±68.6 32 (84.2%) 6 (15.8%)
HIFU sessions	Median (range)	8 (5–16)

Notes: *Tumor size at baseline was measured by CT and MRI imaging in 30 and 14 cases, respectively. Within six patients who evaluated by both imaging modalities, the results from MRI were adopted.

Abbreviations: CT, computed tomography; HIFU, high-intensity focused ultrasound; MRI, magnetic resonance imaging; VAS, visual analogue scale; UICC, Union for International Cancer Control; DCR, disease control rate; KPS, Karnofsky Performance Status.

All patients received at least five HIFU sessions, with median HIFU sessions of 8 (range: 5–16) times.

Safety Of HIFU And Gemox Treatment

All these 38 patients were included in the safety evaluation. During HIFU treatment, upper abdominal discomfort was complained by 4 cases (10.5%), which was disappeared after an adjusted dose or stopping treatment. After HIFU ablation, three patients (7.9%) reported the tolerable liver area pain or low back pain, and two (5.2%) patients with moderate to severe pain required non-steroidal or morphine analgesics for analgesia. Two cases (5.2%) complained fever of <38.5 °C and returned to normal at 1 to 3 days after symptomatic treatment. Two patients (5.2%) with pancreatic head cancer developed obstructive jaundice after treatment. Combined with clinical sign and CT imaging, it was speculated that the necrotic tumor tissue fibrosis was compressed by the common bile duct after treatment. All patients had no complications such as gastrointestinal bleeding, intestinal perforation, pancreatic fistula, pancreatitis, mesenteric artery rupture, skin burning, or embolism.

The chemotherapy toxic side effects were mainly dose-limiting bone marrow suppression (Table 2). Severe digestive tract reaction (nausea and vomiting) is rare due to symptomatic treatment by antiemetic drugs. Hepatic and renal dysfunction were few and mostly mild, of which mainly manifested by elevated levels of alanine aminotransferase and urea nitrogen. No chemotherapy-related deaths occurred. No complications such as pancreatic fistula, gastrointestinal bleeding, pancreatitis, and gastrointestinal perforation occurred.

Clinical Response And CA 19-9 Response

All these patients received at least once CT or MRI scan for response evaluation, of which 23 patients were followed up by CT only, and the other 15 cases were followed up by both CT and MRI. Median follow-up scans were 3 times (range: 1–5). As presented in Table 3 and Figure 1, CR, PR, SD, and PD were observed in 1, 6, 22, and 9 cases, respectively, after HIFU treatment. Objective response rate (ORR, CR + PR) was 18.4% (7/38). Disease control rate (DCR, CR+PR+SD) was 76.3% (29/38). Mean serum CA19-9 level was 247.9±68.6 U/mL before treatment, and decrease to 193.5±59.4 U/mL ($P<0.05$) at six weeks after HIFU treatment. Subgroup analysis by UICC stage revealed no significant difference in the CBR (Chi-square test p=0.470 and 0.098 for clinical response evaluation and CA 19–9 response evaluation, respectively)

CBR Evaluation

Eight cases (21%) with the KPS score of greater than 80 points had no significant pain before treatment or no obvious weight loss. Therefore, the evaluation of pain relief, analgesic reduced, KPS improvement, and weight gain were conducted in 30 cases. As shown in Table 4, the pain relief rate was 90.0% (27/30), the analgesic medication was reduced by 76.6% (23/30), the KPS level was improved by 63.3% (19/30), and the weight gain was 56.6% (17/30), the clinical benefit rate was estimated to be 68.4% (26/38). Among them, the primary manifestation was the decrease in pain intensity. VAS level decreased from 5.86±2.13 before treatment to 2.03±0.51 after treatment significantly

Table 2 Toxic Effects Of HIFU Combined With Chemotherapy In The Treatment Of Advanced Pancreatic Cancer

Toxic Effects	Grade				III–IV(%)	Rate (%)
	I	II	III	IV		
Leukopenia	16	9	4	3	18.4	84.2
Thrombocytopenia	12	7	3	1	10.5	60.5
Hemoglobin reduction	25	4	1	0	2.6	78.9
Hepatic dysfunction	9	2	1	1	5.2	34.2
Renal dysfunction	8	2	0	0	0	26.3
Nausea and vomiting	16	5	1	0	2.6	57.8
Peripheral nerve toxicity	11	3	0	0	0	36.8

Table 3 Best Overall Response And CA 19–9 Response Of Patients

Response	Total (N=38) n (%)	Stage II (n=4) n (%)	Stage III (n=15) n (%)	Stage IV (n=19) n (%)
Best overall response*				
CR	1 (2.6%)	0	1 (6.7%)	0
PR	6 (15.8%)	1 (25.0%)	2 (13.4%)	3 (15.8%)
SD	22 (57.9%)	2 (50.0%)	9 (60.0%)	11 (57.9%)
PD	9 (23.7%)	1 (25.0%)	3 (20.0%)	5 (26.3%)
ORR (CR+PR)	7 (18.4%)	1 (25.0)	3 (20.0%)	3 (15.8%)
DCR (CR+PR+SD)	29 (76.3%)	3 (75.0%)	12 (80.0%)	14 (73.7%)
CA 19–9 Decrease				
>20%	26 (68.4%)	3 (75.0%)	10 (66.7%)	13 (68.4%)
>50%	17 (53.1%)	2 (50.0%)	7 (46.7%)	8 (42.1%)
>90%	11 (34.4%)	1 (25.0%)	4 (26.7%)	6 (31.6%)

Notes: *Response evaluation was performed at one month and three months after HIFU and then 3-month intervals during the first years and 6-month intervals during the remainder of the follow-up phase. Here, the best overall response was reported. In the results of the best overall response, 3 cases were evaluated by both CT and MRI.
Abbreviations: CT, computed tomography; HIFU, high-intensity focused ultrasound; MRI, magnetic resonance imaging; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, objective response rate; DCR, disease control rate.

Table 4 CBR Evaluation Of HIFU Combined With Chemotherapy In The Treatment Of Advanced Pancreatic Cancer

CBR	Total, n (%)	Stage II, n (%)	Stage III, n (%)	Stage IV, n (%)
Valid	26 (68.4%)	2 (50.0%)	11 (73.3%)	13 (68.4%)
Pain relief*	27 (90%)	1 (50.0%)	12 (92.3%)	13 (86.7%)
Analgesic reduction*	23 (76.6%)	2 (100.0%)	10 (76.9%)	11 (73.3%)
KPS improvement*	19 (63.3%)	1 (50.0%)	9 (69.2%)	9 (60.0%)
Weight Gain*	17 (56.6%)	1 (50.0%)	7 (53.8%)	9 (60.0%)
Invalid	12 (31.6%)	2 (50.0%)	4 (26.7%)	6 (32.6%)

Notes: *These items were evaluated in 30 patients by excluding eight cases without any pain, analgesic, KPS reduction, or weight loss.
Abbreviations: CBR, clinical benefit rate; HIFU, high-intensity focused ultrasound; KPS, Karnofsky Performance Status.

($p<0.01$). Subgroup analysis by UICC stage revealed no significant difference in the CBR (Chi-square test p=0.327)

Survival

Within a median follow-up of 15.5 (range: 3.4–24.0) months, the median OS was estimated to be 12.5 months, with 95% CI of 10.3–13.9 months. The 6-month and 12-month OS were 82.13% (95% CI=64.45–91.56%) and 59.34% (95% CI=38.93–47.92%), respectively. Median PFS was 6.7 (95% CI=5.1–9.7) months, and the 6-month and 12-month PFS were 53.91% (36.65–68.36%) and 16.39% (6.14–30.98%), respectively. (Table 5 and Figure 2)

Discussion

Pancreatic cancer is considered to be one of the worst prognostic evaluated, especially for these unresectable cases.

Table 5 Survival Outcome And Subgroup Analyses By The UICC Stage Of Patients Treated With HIFU And Gemox

Survival	Overall (n=38)	Stage II (n=4)	Stage III (n=15)	Stage IV (n=19)	Log-rank p-values
Median OS, months (95% CI)	12.5 (10.3–13.9)	11.5 (5.7-NE)	12.5 (4.8-NE)	12.2 (7.5–14.2)	0.95
6-month OS rate, % (95% CI)	82.13 (64.45–91.56)	75.00 (12.79–96.05)	76.92 (44.21–91.91)	87.50 (58.60–96.72)	-
1-year OS rate, % (95% CI)	59.34 (38.93–47.92)	37.50 (1.10–80.80)	65.93 (31.54–86.04)	59.58 (30.84–79.62)	-
Median PFS months (95% CI)	6.7 (5.1–9.7)	6.2 (4.8-NE)	6.9 (1.7–10.8)	5.7 (3.7–10.4)	0.81
6-month PFS rate, % (95% CI)	53.91 (36.65–68.36)	75.00 (12.79–96.05)	53.33 (26.32–74.38)	48.63 (24.29–69.27)	
1-year PFS rate, % (95% CI)	16.39 (6.14–30.98)	0 (NE-NE)	23.33 (5.92–47.27)	14.19 (2.42–35.88)	

Abbreviations: OS, overall survival; PFS, progression-free survival; HIFU, high-intensity focused ultrasound; CI, confidence interval; UICC, Union for International Cancer Control; NE, not evaluable.

Treatment options with significant efficacy and safety remain to be explored and evaluated,[6] notwithstanding recent advances in chemotherapy and radiation therapy.

HIFU treatment is a newly developed non-invasive technique and applied in the treatment of various malignant tumors in recent years. In China, nearly 10,000 treatment experiences of HIFU ablation had been accumulated in clinical application for the past ten years. Pancreatic cancer, especially advanced pancreatic cancer, has gradually been considered as one of the best indications for HIFU treatment. The technical advantages of HIFU and the characteristics of pancreatic cancer are

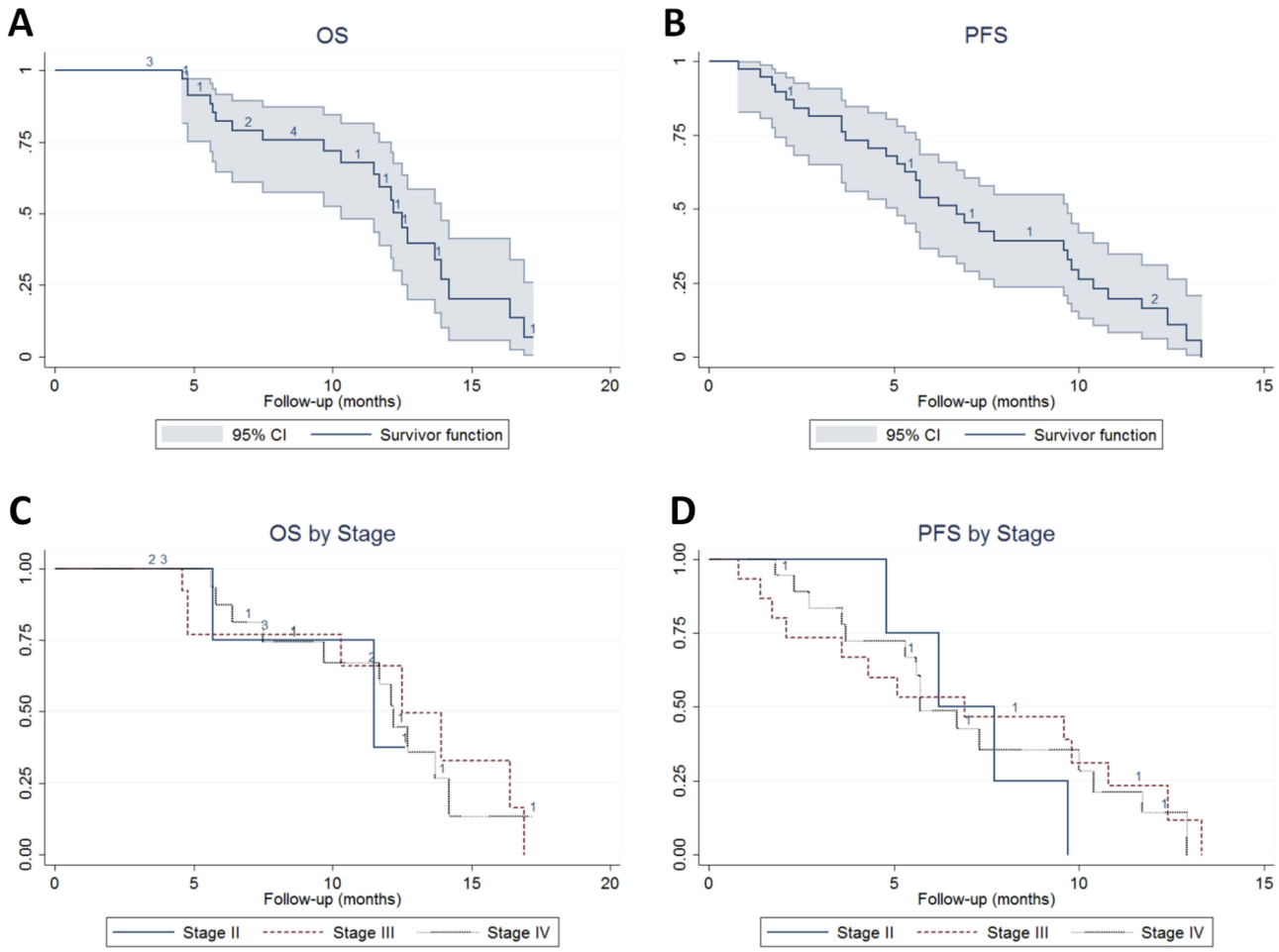

Figure 2 Survival outcome of patients treated with HIFU and Gemox.
Notes: (**A**) OS of the overall cohort; (**B**) PFS of the overall cohort; (**C**) Subgroup analysis of OS by UICC Stage; No significant difference was detected between cases in different stages (Log-rank p = 0.95); (**D**) Subgroup analysis of PFS by UICC Stage; No significant difference was detected between cases in various stages (Log-rank p = 0.95).
Abbreviations: OS, overall survival; PFS, progression-free survival; HIFU, high-intensity focused ultrasound; CI, confidence interval; UICC, Union for International Cancer Control.

compatible:[31] (1) HIFU ablation does not damage the large blood vessels around the lesions, thus avoiding the bleeding events which might occur in surgical resection[38] (2) The pancreas is located in the retroperitoneum and will not move with respiratory movement,[39] which is beneficial to HIFU localization and real-time monitoring. (3) Most of the pancreas tumors are lack of blood supply,[40] which would attenuate the effect of chemotherapeutic drugs. Meanwhile, HIFU ablation in the tissue with low blood supply will avoid the loss of heat, which is conducive to rapidly reaching the lethal temperature of the tumor. (4) Non-invasive characteristics of HIFU treatment ensures the sustainability and reproducibility of patients with pancreatic cancer. However, HIFU ablation is a topical treatment, which would rarely achieve a significant efficacy and long-term survival for cases with metastatic pancreatic cancer. Previous studies have shown that HIFU is synergistic with chemotherapy.[41–43] Thus we adopt the combination therapy to achieve optimal efficacy.

In terms of the adverse events, the main toxic side effects of chemotherapy were myelosuppression and digestive tract reactions, but most of them were mild and tolerated. The complications of HIFU ablation were rare and usually healed themselves. The most common complications reported by patients are local pain and temporary fever. In all the subjects, local mild pain occurred in 3 cases and moderate to severe pain in 2 cases. The leading cause of pain is that when the mass is close to the ribs and the spine, the mechanical force of the ultrasound causes adjacent nerve damage. Skin burn is a complaction of special interset as it was reported by mumerous studies on HIFU. However, our results did not show any evidence of skin burn. This might be attributed to the differences in the type of HIFU equipment used for treatment. Our device (HIFUNIT-9000) adopts dual focus mode, and the energy upon the skin could be reduced effectively during operation compared with other equipment. Besides, we conducted the ablation of each patient in several days to advoid potential complations by energy accumulation, including skin burns. A case of skin blisters was observed, which might be caused by poor performance status and body weight loss. Therefore, performance status of patients during HIFU treatment should be considered to adjust the treatment parameters. Also, the treatment parameters should change with the location, size, blood supply of the tumor, and different combination treatment options, in order to avoid tissue damage caused by excessive power. No gastrointestinal bleeding, gastrointestinal perforation, pancreatic fistula, pancreatitis, peritonitis, mesenteric artery rupture or embolism, or nerve trunk injury were observed. High safety of HIFU provides more options for elderly, frail patients, cases with comorbidities, and patients who are intolerant to conventional treatment.

In the studies of Gemox treatment for pancreatic cancer, the ORR and DCR varied from 10% to 30%, and from 80% to 85%, respectively, and the median OS and PFS were 3.2–15 months, and 2.5–7 months, respectively.[11–14] HIFU monotherapy provided ORR of 14.6% to 77.5% and median OS of 5.4 to 16.2 months.[27,28,44–46] Zhou et al overviewed 241 articles with a total of 653 cases on the HIFU monotherapy for locally advanced pancreatic cancer and revealed that the median OS is 10 months, and the pooled pain remission rate was 71.3%.[23] In theory, HIFU monotherapy and Gemox combination therapy should be superior to the single treatment. However, in our subjects, the ORR and DCR were estimated to be 18.4% and 76.3%, respectively, which were comparable with previous studies. A monocentric retrospective study by Ning et al had evaluated the safety and effectiveness of HIFU combined with gemcitabine (GEM) in 347 pancreatic cancer patients. The median OS was reported to be 7.4 months, with 6-month and 1-year survival rate of 66.3% and 21.32%.[47] As a comparison, the median OS and PFS in present analysis were observed to be 12.5 months and 6.7 months, which seems to be better than prior evidence. Similar superiority of the 6-month and 12-month OS rate were also obtained to be 82.13% and 59.34% in our study. What should be noted is that the patients included in previous studies mentioned above were both local advanced pancreatic cancer, without limit of age. Meanwhile, our study included only elderly cases (>60 years) and some metastatic cases, which might affect the response rate and survival time. Another meta-analysis by Dababou et al in 729 pancreatic cancer patients who treated by HIFU revealed a pain relief rate of 80.95% (459/567).[48] The rate by us was observed as 90%, which might numerically superior to previous result. Therefore, the combination treatment of HIFU and Gemox should be considered to be one of the effective options for elderly patients. It is widely acknowledged that clinical-stage would affect the prognosis of pancreatic cancer patients. Regretfully, subgroup analyses by clinical stage did not revealing any significant difference. It may be caused by low statistical power with small-size of samples, especially only four cases in the stage II.

Some limitations should be acknowledged: (1) This retrospective case series study with a small number of

cases would not provide strong evidence to guide the clinical practice. Our report aims to share the experience of our center in elderly cases. (2).Potential selection bias would exist in our study, which would be one of the intrinsic characteristics of the retrospective study and hard to avoid. (3). Due to the limited number of cases included in this study, some factors which might affect the efficacy of HIFU were not analyzed, including gastrointestinal gas, therapeutic output, and patient tolerance. Therefore, top-level designed trails with a larger sample size are needed. Nevertheless, our investigation has provided a piece of reliable clinical evidence for the new direction of ablation treatment for advanced pancreatic cancer, especially in elderly patients.

In conclusion, elderly patients (≥ 60 years old) with pancreatic cancer would experience tolerable toxicity and obtain good clinical benefit from the combination therapy of HIFU ablation and Gemox. However, more well-designed randomized controlled trials are needed to confirm the efficacy of HIFU-based combination therapy.

Ethical Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Xinhua Hospital Affiliated To Shanghai Jiaotong University School of Medicine (number: 2017-43).

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Author contributions

All authors made substantial contributions to the design and conception of the study, and acquisition, analysis and interpretation of data, and took part in either drafting or revising the manuscript. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure

All the authors declare that there are no conflicts of interest.

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